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L1: Entry 14 of 14

File: USOC

Apr 23, 1991

DOCUMENT-IDENTIFIER: US 5009956 A

TITLE: Phospholipase A2-resistant liposomes

OCR Scanned Text (8):

5,009,956 FIG. 2 graphically depicts the ratio of I-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) versus lysoPC on the outer monolayer. It can be observed from FIG. 2 that this ratio falls off sharply with increasing mol-% of lysoPC and finally remains constant between 20-25 mol-% IYsOPC. FIG. 3 graphically depicts the ratio of lysoPC/POPC in the outer monolayer versus the mol-% of lysoPC. FIG. 4 graphically depicts the amount of POPC hydrolyzed in the first 30 min. versus the mol-% of lysoPC originally present in the POPC/lysoPC vesicles. The amount of POPC hydrolyzed at 30 min. is calculated from the difference in NMR peak integral values between 0 to 30 min. As shown in FIG. 4, the amount of POPC hydrolyzed at 30 min. correlates very well with the ratio of lysoPC to POPC in the outer monolayer (FIG. 3) DETAILED DESCRIPTION OF THE INVENTION 20 Membrane components of formulas I and II are formally derivatives of glyceryl-3-phosphoryl choline, or "dilyso-phosphatidyl choline", which has been di-(1,2-) and mono(I-)acylated, respectively, with fatty acids, e.g., (C10-C30)alkyl-CO2H. Compounds of formulas 1 25 and II are commercially available, e.g., from Sigma Chemical Co., St. Louis, MO and from Avanti Polar Lipids, Inc., Birmingham, AL. Commercially-available compounds of formula I include alpha-lecithin, I-palmitoyl-2-oleoyl-phosphatidylcholine (PC); I-stearoyl-2-arachidonoyl-PC; 1,2-diarachidoyl-PC; 1,2-dicaproyl-PC; 1,2-dielaaidoyl-PC; 1,2-diheptanoyl-PC; 1,2-dilauroyl-PC; 1,2-dilinoleoyl-PC; 1,2-dimyristoyl-PC; 1,2-dioleoyl-PC; 1,2-dipentadecanoyl-PC; 1,2-dipalmitoyl-PC; 1,2-distearoyl-PC; 1,2-diundecanoyl-PC; I-palmitoyl-2-elaidoyl-PC; I-palmitoyl-2-linoleoyl-PC; I-stearoyl-2-oleoyl-PC; I-oleoyl-2-palmitoyl-PC; 1-cleoyl-2-stearoyl-PC. (C10-C30)-fatty acid esters of glyceryl-3-phosphorylcholine wherein the fatty acids contain 1-2 triple bonds can also be used. 40 The corresponding compounds of formula II can be prepared from compounds of formula I by hydrolysis with phospholipase A2, e.g., as disclosed by L. L. M. van Deenen and G. H. de Haas, Biochim. Biophys. Acta, 70, 538 (1963), the disclosure of which is incorporated 45 by reference herein. Glyceryl-3-phosphocholine can also be selectively mono- or di-esterified by techniques well known in the art of organic synthesis. For example, see I. T. Harrison et al., Compendium of Organic Synthetic Methods, Wiley-Interscience, New York, NY 50 (1971), at pages 280-286. As described in detail hereinbelow, small unilamellar vesicle (SUV) liposomes (250-300 k O.D.) can be prepared by dispersing films comprising phospholipids of formulas I and II in water or aqueous buffer, by sonication of the mixture to equilibrium under an inert atmosphere at about 1'-5' C. In a preferred embodiment, the lipid dispersion is sonicated for about 20 min. to 2.0 hours under nitrogen with a Branson tip sonicator model 350, at a power setting of 4. It will be appreciated 60 that other sonication devices may be used to achieve similar results and that equilibrium may be reached in less than 20 min. at a higher power setting. Small unilamellar vesicles can also be prepared by extruding a lipid mixture through a micropore filter having a pore size of about 250-300 k. Larger liposomes can be prepared by extruding the lipid mixture through a larger micropore filter. e.g., of 500, 800 or 1000 k. The optimal mol-% of lysophospholipid required in order to achieve total inhibition of PLA2 hydrolysis

of the membrane can be determined by empirical trials in accord with the detailed example described hereinbelow. It has also been found that preferred amounts of lysophospholipid (II) act to physically stabilize SUVs, as well as to protect them against enzymatic degradation. These stabilizing effects appear to be due to the fact that the lysophospholipid molecule spacially occupies a "cone-shaped" space in the outer layer, thereby fulfilling the geometric packing requirements of highly curved vesicle surfaces. Thus, the lysophospholipid molecules strengthen the walls of SUVs which have highly curved membrane surfaces and act to relieve their internal stress. It is also believed that they make the surface impermeable to enzymes such as PLA2 by blocking access to the C-2 carbon of the glycerol moiety. When liposomes are sonicated until their constituents reach "equilibrium", they have reached a point of stable equilibrium of the mol-% ratios of LPL to PL in the outer layer of the membrane, and of LPL in the outer layer to LPL in the inner layer. When this equilibrium has been reached, optimum stability with respect to PLA2-type hydrolysis is exhibited. EXAMPLE Small Unilamellar POPC/lysoPC Vesicles

A. Methods and Materials I-Palmitoyl-2-oleoyl phosphatidylcholine (POPC) and I-palmitoyl lysophosphatidylcholine (lysoPC) were obtained from Avanti Polar Lipids, Inc. (Birmingham, AL) - D20 (99.8% D) and CDC13 (99.8% D) were obtained from KOR Isotopes (Cambridge, MA). Praseodymium chloride (99.9%) and calcium chloride were obtained from Aldrich Chemical Company (Milwaukee, WI). Snake venom phospholipase A2 (Ophiophagus hannah) was obtained from Miami Serpentarium (Miami, FL) and was used, as such. A single spot on thin-layer chromatography confirmed that purity of POPC and lysoPC (developing solvent, chloroform/methanol/water, 65:35:8). B. Preparation of SUV Chloroform/methanol (1:1 v/v) solutions of the two lipids were mixed in a 25 ml round-bottomed flask. The solvents were removed on a rotary evaporator at 25° C. and the lipid film was thoroughly dried under vacuum for 6.0 hr at 25° C. The lipid film was dispersed in D2O to permit NMR observations, and vortexed for 20 min. The resulting lipid dispersion was sonicated under nitrogen with a Branson tip sonicator model 350, at a power setting of 4. Clearing was usually achieved within 30 min. The sonication vial was kept in an icewater bath at 4° C. during sonication. Metal particles from the probe and any unbroken lipid aggregates were removed by high-speed ultracentrifugation for 1.0 hr. at 105,000 x g on a Beckman model L5-75 ultracentrifuge. Inorganic phosphorus assay of the sediment after centrifugation, by the method of C. H. Fiske and Y. Subbarow, J.B. C, 66, 375 (1925), showed less than 0.5% of phosphorus, indicating that all of the lipid had been converted into SUVs. C. Characterization and Hydrolysis of SUV The SUV prepared were characterized by negative staining electron microscopy. Sixty umoles of POPC and different amounts of lysoPC were present per 1 ml

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L1: Entry 13 of 14

File: USPT

Jan 1, 1991

DOCUMENT-IDENTIFIER: US 4981690 A

TITLE: Liposome-incorporated mepartricin

Brief Summary Text (25):

The composition of matter of the present invention, in a preferred embodiment, consists essentially of mepartricin, a sterol and one or more phospholipids selected from the group consisting of egg phosphatidylcholine, distearylolphosphatidylcholine, dioleoylphosphatidylcholine and dielaidoylphosphatidylcholine. A favored composition is one which comprises the phospholipids and sterol are in a ratio of about 9:1 as well as the mepartricin and combined phospholipids--sterol having a ratio of about 1:10. The liposomal form referred to above is preferably a stable multilamellar vesicle, although other types of liposomes may be utilized.

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L1: Entry 12 of 14

File: USPT

Mar 12, 1991

DOCUMENT-IDENTIFIER: US 4999199 A

**\*\* See image for Certificate of Correction \*\***

TITLE: Pharmaceutical formulations: liposomes incorporating aromatic polyene antibiotics

Detailed Description Text (10):

Candicidin was obtained from Dumex Co. (Copenhagen, Denmark) and was encapsulated in liposomes as follows: The lipids Egg phosphatidylcholine (EggPC), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG) dielaidoylphosphatidylcholine (DEPC) phosphatidylthanolamine (PE), dioleoylphosphatidylcholine (DOPC), distearoylphosphatidylcholine (DSPC), dipalmitoylphosphatidylcholine (DPPC) and cholesterol, were obtained from Avanti Polar lipids (Birmingham, Ala).

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L1: Entry 11 of 14

File: USPT

Nov 10, 1998

DOCUMENT-IDENTIFIER: US 5834012 A

\*\* See image for Certificate of Correction \*\*

TITLE: Lipid complexed topoisomerase I inhibitors

Detailed Description Text (52):

DOTAP complexes well with CPT (Table 2) and forms fluorescent liposomes with CPT, yet when DOTAP is combined with DO-NGPE no liposomes are formed. Therefore, if DOTAP was used with CPT, DO-NGPE is not a desirable component of the liposomes. This led to the exploration of other Dioleoyl (18 : 1) compounds that would complex with CPT (see DOPC, DOPE, DOPG, Dielaidoyl PC) in Table 2. As Table 2 shows, DOTAP, DOPE, and Dielaidoyl PC complex well with CPT. This discovery led to the exploration of Dioleoyl compounds that when combined could both complex with CPT and form liposomes (liposomal CPT). This led to the following formulations (Table 3): (DOPG : DO-NGPE : CPT, DOPE : DOPC : CPT, and DOPC : DOPG : CPT). All of these above formulations form liposomes, but still contain a few CPT crystals. Table 4 follows the same reasoning using mole % ratios of dioleoyl lipids to form liposomal CPT. A liposomal CPT preparation, DOPE : DOPC : DOTAP (40%, 40%, 20%) contains fluorescent liposomes of CPT and very few, if any, CPT crystals. The DOPE:DOPC:DOTAP formulation is a milky liposomal suspension that contains liposomes of various size 5 (75% of the preparation is smaller than one micron in diameter). The larger liposomes fluoresce slightly, while the smaller liposomes (that cannot be seen) aggregate into larger fluorescent liposomes over time.

Detailed Description Paragraph Table (4):

TABLE 4	Liposomal CPT Formulations (Mol. % lipids + 1 Mg CPT)		<u>Liposomes</u> Complexes		Formulation Mol. %		Formed with CPT	
Crystals								
55% DOTAP 20% no +++ few	DOPG 25% egg	PC 55%	DMPC 55% no ++	few DOPG 25%	DOTAP 20% yes ++	few DMPC 25%	NGPE	
DOPC 55% yes + many	DOPG 25%	DOTAP 20%	DOPE 40% yes ++++	none DOPC 40%	DOTAP 20%	OCPC 40% yes +	few DOPC 40%	DOTAP 20%
40% yes ++ few	<u>Dielaidoyl</u> PC 40%	DOTAP 20%						

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L1: Entry 10 of 14

File: USPT

Feb 9, 1999

DOCUMENT-IDENTIFIER: US 5869092 A

**\*\* See image for Certificate of Correction \*\***

TITLE: Prevention of leakage and phase separation during thermotropic phase transition in liposomes and biological cells

Drawing Description Text (7):

FIG. 6 shows two calorimetric scans, one taken of dielaidoylphosphatidylcholine (DEPC) liposomes treated in accordance with the invention and the other of the same liposomes but untreated.

Detailed Description Text (27):

This example illustrates the effect of antifreeze glycoproteins and antifreeze proteins in inhibiting leakage from dielaidoylphosphatidylcholine liposomes during a phase transition.

Detailed Description Text (28):

Liposomes were prepared from dielaidoylphosphatidylcholine (DEPC) vesicles in a conventional manner, except that carboxyfluorescein was included in the forming solution at a concentration of 200 mM and accordingly trapped inside the resulting liposomes as a marker. Once formed, liposomes were sized by extrusion through polycarbonate filters, using the commercial apparatus produced by Avestin, Inc., Ottawa, Ontario, Canada. Excess carboxyfluorescein not trapped by the liposomes was removed by passing the liposomes through a Sephadex column. The resulting liposome suspensions had a liposome concentration of 20 mg/mL.

## CLAIMS:

12. A method in accordance with claim 1 in which said liposomes have lipid components selected from the group consisting of dielaidoylphosphatidylcholine and dimyristoylphosphatidylcholine.

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L1: Entry 7 of 14

File: USPT

Feb 10, 2004

DOCUMENT-IDENTIFIER: US 6689381 B2

TITLE: Liposomal benzoquinazoline thymidylate synthase inhibitor formulations

Detailed Description Text (44):

"Phospholipid" refers to any one phospholipid or combination of phospholipids capable of forming liposomes. Phosphatidylcholines (PC), including those obtained from egg, soy beans or other plant sources or those that are partially or wholly synthetic, or of variable lipid chain length and unsaturation are suitable for use in the present invention. Synthetic, semisynthetic and natural product phosphatidylcholines including, but not limited to, distearoylphosphatidylcholine (DSPC), hydrogenated soy phosphatidylcholine (HSPC), soy phosphatidylcholine (soy PC), egg phosphatidylcholine (egg PC), dioleoylphosphatidylcholine (DOPC), hydrogenated egg phosphatidylcholine (HEPC), dielaidoylphosphatidylcholine (DEPC), dipalmitoylphosphatidylcholine (DPPC) and dimyristoylphosphatidylcholine (DMPC) are suitable phosphatidylcholines for use in this invention. All of these phospholipids are commercially available. Preferred PCs are HSPC and DSPC; the most preferred is HSPC.

## CLAIMS:

2. The liposome of claim 1 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

6. The liposome of claim 2 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

16. The liposome of claim 6 wherein the molar ratio of dielaidoylphosphatidylcholine to cholesterol is about 2:1.

66. The liposome of claim 56 wherein the molar ratio of dielaidoylphosphatidylcholine to cholesterol is about 2:1.

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L1: Entry 7 of 14

File: USPT

Feb 10, 2004

US-PAT-NO: 6689381

DOCUMENT-IDENTIFIER: US 6689381 B2

TITLE: Liposomal benzoquinazoline thymidylate synthase inhibitor formulations

DATE-ISSUED: February 10, 2004

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Jensen; Gerard M.	Brea	CA		

US-CL-CURRENT: 424/450; 264/4.1, 264/4.3, 514/248

## CLAIMS:

We claim:

1. A liposome comprising at least one phosphatidylcholine, a cholesterol, and (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid.

2. The liposome of claim 1 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

3. The liposome of claim 2 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine.

4. The liposome of claim 2 wherein said phosphatidylcholine is soy phosphatidylcholine.

5. The liposome of claim 2 wherein said phosphatidylcholine is dioleoylphosphatidylcholine.

6. The liposome of claim 2 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

7. The liposome of claim 2 wherein said liposome further comprises phosphatidylglycerol.

8. The liposome of claim 7 wherein said hydrogenated soy phosphatidylcholine, cholesterol and phosphatidylglycerol are in a molar ratio of about 2:1:0.1.
9. The liposome of claim 3 wherein the hydrogenated soy phosphatidylcholine to cholesterol molar ratio is from about 5:1 to 2:1.5.
10. The liposome of claim 9 wherein said molar ratio is about 2:1.
11. The liposome of claim 9 wherein said molar ratio is about 4:1.
12. The liposome of claim 10 wherein said liposome is unilamellar and less than 100 nm.
13. The liposome of claim 12 wherein said hydrogenated soy phosphatidylcholine to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from about 5:1 to 75:1.
14. The liposome of claim 4 wherein the molar ratio of soy phosphatidylcholine to cholesterol is about 2:1.
15. The liposome of claim 5 wherein the molar ratio of dioleoylphosphatidylchoine to cholesterol is about 2:1.
16. The liposome of claim 6 wherein the molar ratio of dielaidoylphosphatidylcholine to cholesterol is about 2:1.
17. The liposome of claim 12 wherein said hydrogenated soy phosphatidylcholine to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from about 8:1 to 20:1.
18. A liposome comprising (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid, encapsulated in a liposome, wherein said liposome is comprised of hydrogenated soy phosphatidylcholine (HSPC) and cholesterol and wherein HSPC:cholesterol are in a molar ratio of about 2:1, and wherein the HSPC to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from 8:1 to 20:1, and wherein said liposome is unilamllar having a size of less than 100 nm.
19. The composition of claim 1 produced by the process comprising: a) forming a lipid film or powder comprised of phosphatidylcholine and cholesterol; b) hydrating said lipid film or powder with an aqueous solution containing (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid; c) applying energy whereby liposomes that are unilamellar and less than 100 nm are obtained; d) cross-filtering against an aqueous solution to remove unencapsulated (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid whereby liposomes containing (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid are obtained.
20. The composition of claim 19 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine,

hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

21. The composition of claim 20 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine.

22. The composition of claim 20 wherein said phosphatidylcholine is soy phosphatidylcholine.

23. The composition of claim 20 wherein said phosphatidylcholine is dioleoylphosphatidylcholine.

24. The composition of claim 20 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

25. The composition of claim 20 wherein said liposome further comprises phosphatidylglycerol.

26. The composition of claim 19 wherein said energy is applied by a homogenizer.

27. The composition of claim 21 wherein the hydrogenated soy phosphatidylcholine to cholesterol molar ratio is from about 5:1 to 2:1.5.

28. The composition of claim 27 wherein said molar ratio is about 2:1.

29. The composition of claim 27 wherein said molar ratio is about 4:1.

30. The composition of claim 28 wherein said liposome is unilamellar and less than 100 nm.

31. The composition of claim 30 wherein said hydrogenated soy phosphatidylcholine to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from about 5:1 to 75:1.

32. The composition of claim 31 wherein said hydrogenated soy phosphatidylcholine to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from about 8:1 to 20:1.

33. The composition of claim 19 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine (HSPC), and wherein said HSPC:cholesterol are in a molar ratio of about 2:1, and wherein the HSPC to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolyl)glutaric acid molar ratio is from 8:1 to 20:1.

34. A process for making liposomes comprising (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid, said process comprising: a) forming a lipid film or powder comprised of phosphatidylcholine and cholesterol; b) hydrating said lipid film or powder with an aqueous solution containing (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid; c) applying energy whereby liposomes that are unilamellar and less than 100 nm are obtained; d) cross-filtering against an aqueous solution

to remove unencapsulated (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid, whereby liposomes containing (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid are obtained.

35. The process of claim 34 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

36. The process of claim 35 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine.

37. The process of claim 35 wherein said phosphatidylcholine is soy phosphatidylcholine.

38. The process of claim 35 wherein said phosphatidylcholine is dioleoylphosphatidylcholine.

39. The process of claim 35 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

40. The process of claim 35 wherein said liposome further comprises phosphatidylglycerol.

41. The process of claim 34 wherein said energy is applied by a homogenizer.

42. The process of claim 36 wherein the hydrogenated soy phosphatidylcholine to cholesterol molar ratio is from about 5:1 to 2:1.5.

43. The process of claim 42 wherein said molar ratio is about 2:1.

44. The process of claim 42 wherein said molar ratio is about 4:1.

45. The process of claim 43 wherein said liposome is unilamellar and less than 100 nm.

46. The process of claim 45 wherein said hydrogenated soy phosphatidylcholine to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from about 5:1 to 75:1.

47. The process of claim 46 wherein said hydrogenated soy phosphatidylcholine to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from about 8:1 to 20:1.

48. The process of claim 34 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine (HSPC), and wherein said HSPC:cholesterol are in a molar ratio of about 2:1, and wherein the HSPC to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from 8:1 to 20:1.

49. A method of inhibiting the growth of a tumor comprising the administration

of a therapeutic or effective amount of the composition of claim 1 to a tumor.

50. The method of claim 49 wherein said tumor is drug resistant or drug sensitive.

51. The method of claim 49 wherein said tumor is from a cancer selected from the group consisting of ovarian, lung, colorectal, breast, head and neck, prostate, uteran, glioblastoma, and sarcoma.

52. The method of claim 51 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

53. The method of claim 52 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine.

54. The method of claim 52 wherein said phosphatidylcholine is soy phosphatidylcholine.

55. The method of claim 52 wherein said phosphatidylcholine is dioleoylphosphatidylcholine.

56. The method of claim 52 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

57. The method of claim 52 wherein said liposome further comprises phosphatidylglycerol.

58. The method of claim 57 wherein said hydrogenated soy phosphatidylcholine, cholesterol and phosphatidylglycerol are in a molar ratio of about 2:1:0.1.

59. The method of claim 53 wherein the hydrogenated soy phosphatidylcholine to cholesterol molar ratio is from about 5:1 to 2:1.5.

60. The method of claim 59 wherein said molar ratio is about 2:1.

61. The method of claim 59 wherein said molar ratio is about 4:1.

62. The method of claim 60 wherein said liposome is unilamellar and less than 100 nm.

63. The method of claim 62 wherein said hydrogenated soy phosphatidylcholine to (S)-2-(5-(((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from about 5:1 to 75:1.

64. The liposome of claim 54 wherein the molar ratio of soy phosphatidylcholine to cholesterol is about 2:1.

65. The liposome of claim 55 wherein the molar ratio of dioleoylphosphatidylchoine to cholesterol is about 2:1.

66. The liposome of claim 56 wherein the molar ratio of

dielaidoylphosphatidylcholine to cholesterol is about 2:1.

67. The method of claim 62 wherein said hydrogenated soy phosphatidylcholine to (S)-2-(5-((1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-methyl)amino)-1-oxo-2-isoindolinyl)glutaric acid molar ratio is from about 8:1 to 20:1.

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File: PGPB

Mar 21, 2002

DOCUMENT-IDENTIFIER: US 20020034538 A1

TITLE: Liposomal benzoquinazoline thymidylate synthase inhibitor formulations

Detail Description Paragraph:

[0076] "Phospholipid" refers to any one phospholipid or combination of phospholipids capable of forming liposomes. Phosphatidylcholines (PC), including those obtained from egg, soy beans or other plant sources or those that are partially or wholly synthetic, or of variable lipid chain length and unsaturation are suitable for use in the present invention. Synthetic, semisynthetic and natural product phosphatidylcholines including, but not limited to, distearoylphosphatidylcholine (DSPC), hydrogenated soy phosphatidylcholine (HSPC), soy phosphatidylcholine (soy PC), egg phosphatidylcholine (egg PC), dioleoylphosphatidylcholine (DOPC), hydrogenated egg phosphatidylcholine (HEPC), dielaidoylphosphatidylcholine (DEPC), dipalmitoylphosphatidylcholine (DPPC) and dimyristoylphosphatidylcholine (DMPC) are suitable phosphatidylcholines for use in this invention. All of these phospholipids are commercially available. Preferred PCs are HSPC and DSPC; the most preferred is HSPC.

## CLAIMS:

2. The liposome of claim 1 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

6. The liposome of claim 2 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

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